

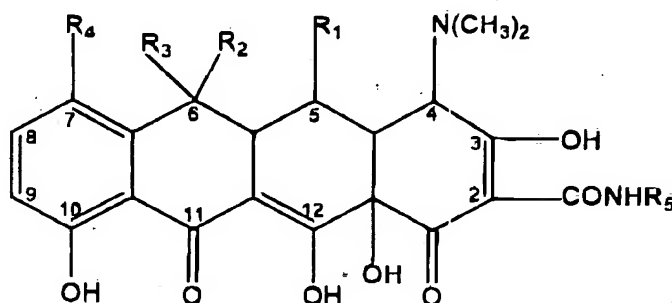
U.S.S.N. 10/007,197

Filed: December 4, 2001

RESPONSE TO RESTRICTION REQUIREMENT

APPENDIX: Marked up Copy of Claims as Pending

1. (amended) A pharmaceutical composition comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

3. The composition of claim 2 wherein R₁ and R₂ are hydrogen or a hydroxyl group; R₃ is hydrogen or a methyl group; R₄ is a hydrogen atom, a halogen, or a nitrogen containing entity; and R₅ is a hydrogen atom, or nitrogen containing ring structure.
4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

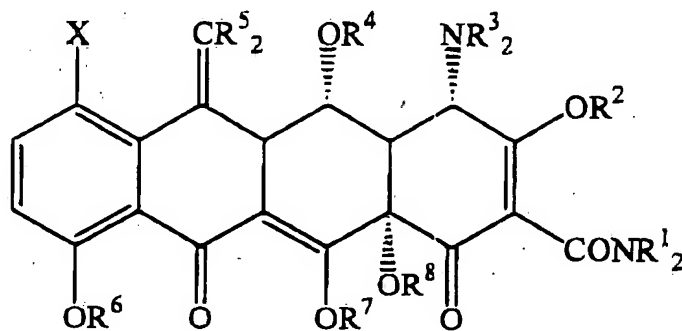
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RESPONSE TO RESTRICTION REQUIREMENT

5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.

6. The composition of claim 2 having the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H; wherein R^3 is CH_3 ; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

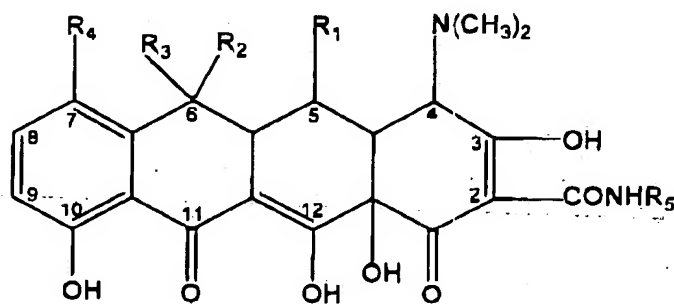
9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.

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10. The composition of claim 9 wherein the tetracycline is formulated as a dry powder.
11. The composition of claim 1 wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered to the mouth and then swallowed.
13. (amended) The composition of claim 1 wherein the polyvalent metal ion is calcium or magnesium.
14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.
15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

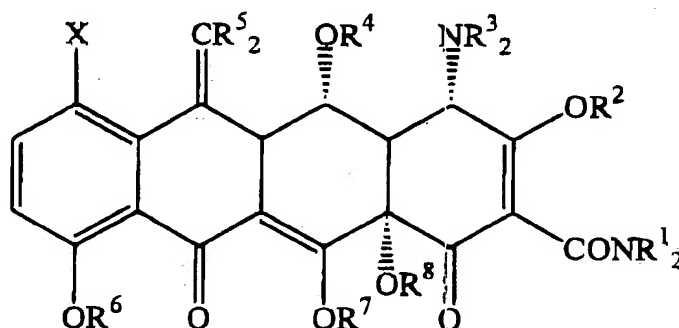
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17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity and R_5 is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

19. The method of claim 18 wherein the tetracycline is meclocycline, wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H;

wherein R^3 is CH₃; and wherein X is a chloro group.

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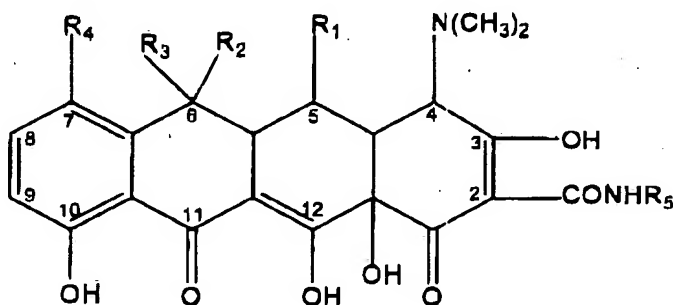
20. The method of claim 15 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.
21. (amended) The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for [adminstration] administration of the tetracycline to the patient.
22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.
23. The method of claim 15 wherein the patient is treated between one and six times daily.
24. (three times amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising
- formulating an effective amount to prevent or treat mucositis of a [tetracycline]
- tetracycline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally [adminstered] administered in a carrier for topical administration to the mucosa.

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RESPONSE TO RESTRICTION REQUIREMENT**APPENDIX: Clean Copy of Claims as Pending**

1. (amended) A pharmaceutical composition comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

3. The composition of claim 2 wherein R₁ and R₂ are hydrogen or a hydroxyl group; R₃ is hydrogen or a methyl group; R₄ is a hydrogen atom, a halogen, or a nitrogen containing entity; and R₅ is a hydrogen atom, or nitrogen containing ring structure.
4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

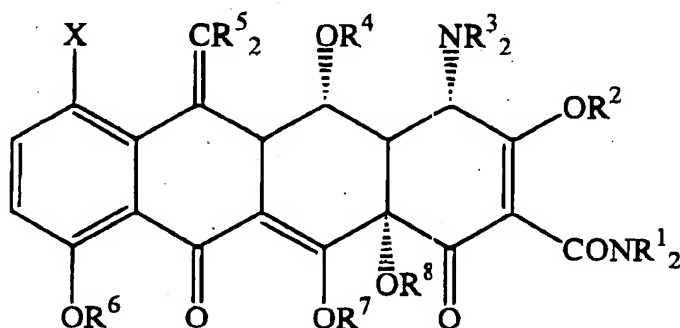
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RESPONSE TO RESTRICTION REQUIREMENT

5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.

6. The composition of claim 2 having the following structure:



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ can be H, C1-C3 alkyl, phenyl, and aryl groups; and wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R¹, R², R⁴, R⁵, R⁶, R⁷, and R⁸ are H; wherein R³ is CH₃; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

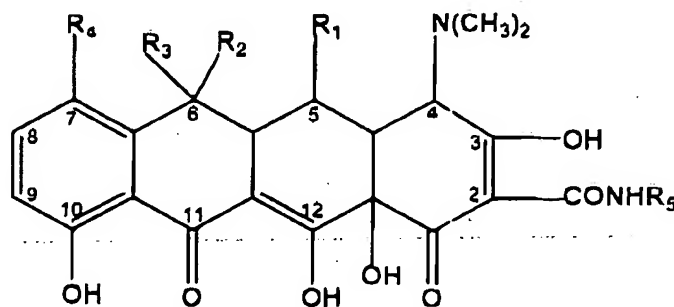
9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.

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13. (amended) The composition of claim 1 wherein the polyvalent metal ion is calcium or magnesium.
14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.
15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R₁-R₅ may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

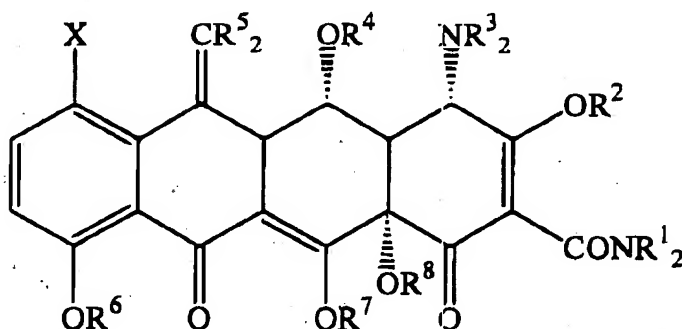
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17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity and R_5 is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

19. The method of claim 18 wherein the tetracycline is meclocycline, wherein R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , and R^8 are H; wherein R^3 is CH_3 ; and wherein X is a chloro group.

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20. The method of claim 15 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

C1
21. (amended) The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for administration of the tetracycline to the patient.

22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.

23. The method of claim 15 wherein the patient is treated between one and six times daily.

C2
24. (three times amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising
formulating an effective amount to prevent or treat mucositis of a tetracycline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered in a carrier for topical administration to the mucosa.

ATL1 #557737 v1